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American Chemistry Council *Good Chemistry Makes It Possible*

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August 20, 2002

Via: Messenger Delivery

Document Control Officer (MC-7404)
Office of Pollution Prevention and Toxics
Room 6428
U.S. Environmental Protection Agency
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Toxic Substances Control Act- Section 8e

Dear Sir or Madam:

The Ethylene Oxide/Ethylene Glycols Panel (Panel) of the American Chemistry Council, on behalf of its member companies[1], submits this information to inform EPA of two revised draft reports of epidemiology studies related to ethylene oxide (EO)[2] conducted by the National Institute of Occupational Safety and Health (NIOSH). This letter supplements our letter of May 28, 2002 (attached). The Panel received these revised, draft reports as part of an ongoing peer review of the studies. The Panel understands that NIOSH has submitted these studies for consideration of publication in the near future.

The Panel has not reached a determination whether the material submitted reasonably supports the conclusion that a substantial risk of injury to health or the environment is presented. This letter and the attached revised studies are being submitted in accordance with TSCA Section 8e for your review.

[1] The members of the Panel are: Abbott Laboratories, Arc Chemical (Balchem), BASF Corporation, Bayer Corporation, Celanese Chemicals on behalf of itself and Old World Industries, The Dow Chemical Company, Eastman Chemical Company, Equistar Chemicals LP, Huntsman Corporation, Honeywell, Sasol North America Inc, Shell Chemical LP, and Sunoco, Inc. The Panel is the successor organization to the Ethylene Oxide Industry Council (EOIC) of the American Chemistry Council.

[2] The CAS Number for Ethylene Oxide is 75-21-8

The following studies are being submitted:

1. **Mortality analysis in a cohort of 18,235 ethylene-oxide exposed workers: follow up extended from 1987 to 1998 by Steenland K, Stayner L and Deddens J.**

2. **Ethylene oxide and breast cancer incidence in a cohort study of 7576 women by Steenland K, Whelan E, Deddens J, Stayner L and Ward E.**

If you have any questions, please call Bill Gulledge, Manager of the EOIC at (703) 741-5613, or e-mail him at william_gulledge@americanchemistry.com.

Sincerely yours,

Barbara Francis

Barbara J. Francis
Managing Director, CHEMSTAR

Attachments: Mortality analysis in a cohort of 18,235 ethylene-oxide exposed workers: follow up extended from 1987 to 1998 by Steenland K, Stayner L and Deddens J.; Ethylene oxide and breast cancer incidence in a cohort study of 7576 women by Steenland K, Whelan E, Deddens J, Stayner L and Ward E.; Letter from Barbara J. Francis to Document Control Officer dated May 28, 2002.

American Chemistry Council *Good Chemistry Makes It Possible*

May 28, 2002

Via: Messenger Delivery

Document Control Officer (MC-7404)
Office of Pollution Prevention and Toxics
Room 6428
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Re: Toxic Substances Control Act- Section 8e

Dear Sir or Madam:

The Ethylene Oxide Industry Council (EOIC) of the American Chemistry Council, on behalf of its member companies[1], submits this information to inform EPA of two draft reports of epidemiology studies related to ethylene oxide (EO)[2] conducted by the National Institute of Occupational Safety and Health (NIOSH). The EOIC received these draft reports as part of an on-going peer review of the studies. The EOIC understands that NIOSH, after receiving comments from the peer review, intends to publish these studies in the near future.

The EOIC has not reached a determination whether the material submitted reasonably supports the conclusion that a substantial risk of injury to health or the environment is presented. This letter and the attached studies are being submitted in accordance with TSCA Section 8e for your review.

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Barbara Francis

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Enclosures

Ethylene oxide and breast cancer incidence in a cohort study of 7576 women

Kyle Steenland[1]

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James Deddens[1]

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July 2002

Acknowledgements: Comments on the manuscript were kindly provided by Tom Smith, Ellen Eisen, and Louise Brinton

Keywords: ethylene oxide, breast cancer

Abstract

Background: Ethylene oxide (ETO) is a sterilant gas considered to be a human carcinogen, due primarily to excess hematopoetic cancer in exposed cohorts. ETO causes mammary tumors in mice, and has been associated with breast cancer incidence in one small epidemiologic study.

Methods: We have studied breast cancer incidence in a cohort of 7,576 women employed for at least one year and exposed while working in commercial sterilization facilities. Breast cancer incidence (n=319) was ascertained via interview, death certificates, cancer registries, and medical records. Interviews were obtained for 68% of the cohort.

Results: The standardized incidence ratio (SIR) for incident breast cancer in the whole cohort using external referent rates (SEER) was 0.87 (0.77-0.97), increasing 0.93 (0.83-1.04) after excluding in-situ cases (6% of cases). The rate ratio for those in the top quintile of cumulative exposure, with a 15 year lag, was 1.27 (0.94-1.69), or 1.34 (0.95-1.83) excluding in-situ cases. A positive trend in SIRs was seen with cumulative exposure with a 15-year lag (p=0.002). Breast cancer incidence in the whole cohort was under-ascertained due to incomplete response and lack of complete coverage by state cancer registries. In internal nested case-control analyses, a positive exposure-response was found with the log of cumulative exposure with a 15-year lag (p=0.05); the top quintile had an odds ratio of 1.74 (1.16-2.65). Analyses restricted to those with interviews controlling for parity and family history again found a positive exposure-response with the log of cumulative exposure (p=.03).

Conclusions: Our data suggest that ETO is associated with breast cancer, but the case is not conclusive due to inconsistencies in exposure-response trends and possible biases due to non-response and incomplete cancer ascertainment.

Introduction

Ethylene oxide (ETO) is widely used as a sterilant gas and an industrial chemical. NIOSH has estimated that approximately 270,000 people were exposed in the US in the 1980s, principally in hospitals (96,000) and commercial sterilization (21,000)[1] ETO is a direct-alkylating agent which causes increased chromosomal aberrations and sister-chromatid exchange [2]. Inhaled ETO is quickly absorbed in the lungs and distributed rapidly throughout all tissues; it forms dose-related hemoglobin adducts in people and rodents, and dose-related DNA adducts in rodents[2]. The International Agency for Research on Cancer (IARC) has determined that ETO is a definite (Group 1) human carcinogen, based on limited evidence from epidemiologic studies showing increased hematopoietic and supported by positive human cytogenetic evidence, and on sufficient evidence from animal studies for hematopoietic and other cancers[2].

Besides hematopoetic cancer, more recently there has been concern that ETO might also be linked to breast cancer, based on limited evidence. Norman et al.[3] found a statistically significant two-fold increase in breast cancer incidence based on 12 observed cases among women exposed at a commercial sterilization plant. A cluster of breast cancers was observed among Hungarian hospital workers exposed to ETO[4]. Furthermore, animal data indicated that ETO caused mammary tumors in mice[2], although not in rats. However, two other small incidence studies (together based on fewer than 10 cases) did not show an excess of breast cancer [5-6]. Two mortality studies, one small[7] (4 breast cancer deaths) and one large[8] (a NIOSH study of 10,000 women, 42 breast cancer deaths) also failed to show an excess. Because breast cancer mortality is a less is a less sensitive endpoint than breast cancer incidence, we have conducted a breast cancer incidence study of 7,576 women from the NIOSH cohort employed for at least one

year, to investigate further the possibility that ETO is associated with breast cancer.

Methods

We sought cancer incidence information for 7,576 women states (76% of the entire cohort) from the NIOSH cohort who had worked for at least one year at one of 14 different plants, located in eleven. The restriction to those with at least one year employment was motivated by cost considerations and the greater difficulty of locating women with short term employment.

We sent a written questionnaire to all women, or their next-of-kin (18% of the cohort had died), for whom we could find valid addresses. After two mailings and a reminder postcard, we called non-respondents, at varying times a day and days of the week. When possible, the interview was then conducted by phone. Addresses and telephone numbers were identified using a variety of strategies including the Internal Revenue Service, the U.S. Postal Service, motor vehicle registration, credit bureaus, and telephone number look-up services. The interview asked about ethnicity, education, height, weight (currently and at age 20), longest job, menstrual and reproductive history (including number and dates of pregnancies, and pregnancy outcomes), use of hormones, smoking history, alcohol history, diet, and cancer history (with extra detail on breast cancer).

Breast cancer ascertainment was also conducted via death certificates and cancer registries. Cancer registries were available in nine of the eleven states in which plants were located, but often for limited periods of time (Texas 1992, 1995-1997, Georgia 1975-1998 for Atlanta area, 1995-1998 for entire state, Kentucky 1991-1998, Maryland 1992, 1998, Florida

1981-1998, New Jersey 1979-1998, Connecticut 1935-1998, South Carolina 1996-1998, New York 1976-1998). We matched women who had worked in a given state or contiguous state against cancer registries for that state; for Florida we sent the entire cohort under the assumption that women from any state may have retired there.

Medical record confirmation was sought for all reported cancers reported on interview. We also sought medical records for all decedents who died of cancer.

Mortality follow-up was extended beyond the previous 12/31/1987 until 12/31/1998, via Social Security, the Internal Revenue Service, and the National Death Index (NDI). Causes of death were obtained from NDI. Vital status for deaths prior to the existence of NDI (prior to 1979) were identified by Social Security and Internal Revenue Service records, and causes of death were obtained via death certificates obtained from states.

Follow-up for breast cancer incidence was likewise terminated as of 12/31/1998. Dates of diagnosis were obtained from self-report, medical record, cancer registry, or next-of-kin. In case of multiple dates the earliest and/or the date considered most valid was used. For decedents for whom no other source was available, date of death was used as date of diagnosis. If a women or her next-of-kin reported breast cancer but this report was specifically contradicted by medical record or cancer registry data, this woman was not included in the analysis as a case (n=6). If a women or their next-of-kin did not report breast cancer on interview but breast cancer was found in the medical record or cancer registry record, then these women were included as a case (n=25).

Estimated exposures over time for this cohort had been developed previously, based on a large number of measurements coupled with data on historical process changes[9]. Exposure

estimates covered all years during which employees were exposed, and were derived from a model which explained 85% of the variance of the observed sampling data. One small plant in the study (19 women with more than 1 year employment, 0.3% of the cohort) lacked exposure estimates, and was excluded from exposure-response analyses.

Work history data had been gathered originally in the mid-1980s. Some plants in the study continued using ETO after this point, and for them we gathered additional information on the date-last-employed for those who had been employed at the time work history was collected (25% of the cohort). Work history for these women was extended until the date-last-employed at the plant in question; it was assumed that they did not change jobs and that the level of ETO exposure remained the same as in their last job in the mid-1980s. Cumulative exposure calculated with and without the extended work histories differed little because exposures were very low by the mid-1980s.

Breast cancer incidence was analyzed in the entire cohort (n=7,576), as well as for the subset of subjects with interview data (5,139, 68%). In the latter analyses we were able to adjust for potential confounders, i.e, other variables associated with breast cancer. Ascertainment of breast cancer in the entire cohort was known to be incomplete, because some women did not have interviews and did not live in states with cancer registries, although it was not possible to estimate the degree of under-ascertainment. Breast cancer ascertainment in the sub-cohort with interviews was considered complete.

Life-table analyses of the entire cohort were done using the NIOSH Life Table Analysis system[10] (www.cdc.gov/niosh/ltdoc.html), using referent rates developed from SEER (Surveillance, Epidemiology, and End Results) data for the period 1970-1999, for invasive

female breast cancer (ICD 9th revision code 174) and in-situ breast cancer (ICD 9th revision code 233.0). The SEER data represent approximately 10% of the US population.

Analyses using SEER referent rates produced SIRs (standardized incidence ratios) by categories of the cumulative exposure (ETO ppm-days), stratified by age (5 year categories), calendar time (5 year categories), and race/ethnicity (white and nonwhite). Followup time began in 1970 when the SEER rates begin, or one year after first employment, or at the date of first exposure plus 90 days (a requirement for cohort entry in the original study), whichever was later. Followup continued until date of death (or diagnosis, for breast cancer cases), end-of-study (12/31/1998), or date-last-observed for those lost-to-followup, whichever was earliest.

Categorical analyses by cumulative exposure (ETO ppm-days) using data from the life table analyses were done by quintiles, based on the cases' cumulative exposure. Analyses with a 15 year lag were also conducted; a 15 year lag was chosen based on having the best fit to the data in Cox regression analyses (see below). A 15 year lag discounts all exposure occurring with the last 15 years, and in some instances results in a case having no exposure ("lagged out"). Quintiles in lagged analyses were formed based on the cumulative exposure of all cases not "lagged out".

Trend tests for trends in SIRs with cumulative exposure (in which the lowest exposed group was the referent) via Poisson regression (SAS GENMOD[11]). For analyses using the log of cumulative exposure with a lag, a cumulative exposure of 1 ppm-day was added to everyone's cumulative exposure to avoid taking the logarithm of 0.

Breast cancer-in-situ was reported for 6% of the cases (20/319). In situ and invasive cancer cases were analyzed separately when using external referent rates (SEER rates), and

results then combined. In situ cases were likewise included in internal Cox regression analysis. Results of analyses did not differ greatly with the inclusion or exclusion of in-situ cases.

Internal exposure-response analyses using a nested case-control design were conducted using Cox regression procedure for the entire cohort and for the sub-cohort with interviews. Analyses were done using the SAS PHREG procedure[11]. In these analyses the time variable was age (effectively matching on age), and risk sets were constructed in which 100 randomly selected controls were chosen for each case from the pool of all those who survived without breast cancer to at least the age of the index case; 100 controls has been shown to be sufficient to obtain a good approximation of the rate ratio obtained using all possible controls (the full risk set), with approximately the same precision[12]. Cases and controls were matched on race (white/non-white). Exposure in these analyses was truncated if it extended beyond the age of the case failure.

For the analysis of the sub-cohort with interviews, variables of interest from the interview were those thought a priori to be associated with breast cancer and hence to be possible confounders, including body mass index, breast cancer in a first-degree relative, parity, menopausal status, age at menopause, age at menarche, socioeconomic status, and diet.

Exposure-response analyses in Cox regression focused on cumulative exposure or the log of cumulative exposure, with or without a lag for exposure. The log of cumulative exposure tends to reduce the influence of very high exposures in skewed exposure distributions, and sometimes improves fit over untransformed cumulative exposure. We also tried models using peak exposure (highest one time exposure) or average exposure (cumulative exposure divided by duration of exposure).

To investigate further the shape of the exposure-response curve, we conducted a restricted cubic-spline analysis with 6 knots. This analysis fitted a cubic exposure-response curve between knots, while fitting a linear model before and after the first and last knots[13].

Results

Completed interviews were obtained for 5,139 (68%) of the 7,576 women in the cohort. The principal reason for no interview was inability to locate the respondent (22%), rather than refusal (7%), or failure to respond after repeated attempts (3%). Reasons for not locating women or their next-of-kin included a lack of good addresses for tracing next-of-kin of deceased subjects (we had no SSNs, the best identifier, for next-of-kin), and the lack of recent or valid addresses for live subjects provided from IRS or credit bureaus (often several years out of date).

Of the entire cohort, 1327 (18%) had died. Interviews were available (from next-of-kin) for 55% of decedents, compared to 71% among the living. Non-respondents had a median year of birth of 1937, and had a median cumulative dose to ETO of 8.0 ppm-years; the corresponding figures for respondents were 1938 and 8.6 ppm-years. While the level of non-response (32%) is of concern, we attempted to determine breast cancer incidence for the entire cohort via sources other than the interview, and a number of analyses were based on the entire cohort. Furthermore, results for the entire cohort (without data on breast cancer risk factors) were similar to the results for the sub-cohort with interviews (with covariate data).

There were 319 incident breast cancers identified among the cohort through the end of 1998, who were eligible for the study (diagnosed after one year after first employment and 90 days exposure). Table 1 provides information regarding the source of these 319 cases. Thirty-

nine percent (124/319) of these cases had died by the end of 1998. Six percent were carcinoma-in-situ cases (n=20). Seventy-three percent (n=233) had interview data.

Table 2 provides some descriptive information on cases and non-cases from among those who had interview data. Cases were older, had fewer children, and were more likely to have had a first degree relative with breast cancer.

Table 3 provides the results of the life table analysis of breast cancer incidence for the whole cohort. Overall the cohort had a standardized incidence ratio (SIR) of 0.87 (0.94 when in-situ cases were excluded. However, the true number of breast cancers was under-ascerttained, so that the SIR based on external SEER comparison rates is underestimated. Regarding exposure-response trends, for the data with a 15 year lag there is a positive trend of higher SIRs ratios with higher cumulative exposure (p= 0.002 for cumulative exposure, p=0.05 using the log of cumulative exposure). For the unlagged data, the trend with cumulative exposure was less marked (p=0.16 for cumulative exposure, p=0.08 using the log of exposure).

Cox regression results for using all cases (319 cases, including 20 in-situ cases) are shown in Table 4 (adjusted only for year of birth and age). Results of categorical analyses are similar to the Poisson analyses of Table 3, as expected. In categorical analyses using a 15-year lag, the top quintile had an odds ratio of 1.74 (95% CI 1.16-2.65). The best fitting model with exposure as a continuous variable was one using the log of cumulative exposure, lagged 15 years (p=0.05). However, a model using duration of exposure with a 15 year lag) fit slightly better than the model using cumulative exposure to ETO. Duration of exposure and cumulative exposure are correlated (Spearman correlation coefficient 0.36). Models using peak or average exposure did not fit as well and are not shown.

Cox regression results for those with interviews (n=5,139, 233 cases) are shown in Table 5. These models are adjusted for nulliparity (any children versus none, odds ratio 0.79, 95% CI 0.55-1.13), breast cancer in a first degree relative (odds ratio 1.60, 95% CI 1.13-2.28), and year of birth (quartiles, earliest quartile as referent, rate ratios 1.00, 1.10 (95% CI 0.71-1.69), 1.55 (95% CI 0.94-2.54), 1.83 (95% CI 0.98-3.41)). Other variables tested did not predict the outcome nor did they act as confounders and they were not included in final models. The results in Table 5 are concordant with Table 4, although exposure response coefficients were slightly higher and the models using the log of cumulative exposure (lagged 15 years) and untransformed cumulative exposure (lagged 15 years) fit about equally well. Duration of exposure (with a 15 year lag) again fit slightly better than cumulative exposure to ETO in a model using continuous variables.

Of the 233 cases with interviews, menopausal status was unknown or missing for 38, was pre-menopausal for 28, and was post-menopausal for 167. Using a model with log cumulative exposure (15 year lag), year of birth, breast cancer in first degree relatives, and parity, the exposure-response coefficient was 0.051 (s.e. 0.024, p=0.04) for post-menopausal women, and 0.036 (s.e. 0.041, p=0.34) for pre-menopausal women We also tried a model adding a variable for age at menopause in the analysis of post-menopausal women, but this variable was not a significant predictor and was omitted.

The Figure shows the exposure-response curve for the full cohort (n=7576, 319 cases) using different models, as well as the categorical results.

While biological considerations do not generally favor the possibility of thresholds for carcinogens (exposure levels below which there is no risk), categorical analyses suggested that

excess risk might be limited to only those in the top one or two quintiles of exposure. We therefore tested a threshold model, in which we assumed no increased risk for different intervals, followed by increased risk based on the model using the log of cumulative exposure (15 year lag). The best fit occurred for a models with a threshold of 6.2 log ppm-days (15 year lag), suggesting that there was no risk for under approximately 1.3 years of exposure at the current standard of 1ppm (assuming a period of 15 years after first exposure before risk occurs). This threshold model fit only slightly better (improvement in model likelihood 1.9) than the non-threshold model with log of cumulative exposure (15 year lag), and this improvement was not statistically significant at the 0.05 level.

The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure. Further categorical analyses using deciles of cumulative exposure (with a 15 year lag) rather than quintiles revealed that the 8th decile had no excess risk (odds ratios by decile versus those lagged out, 0.88, 1.35, 1.00, 1.00, 1.33, 1.22, 1.40, 1.03, 1.68, 1.82). Such inconsistency could be due to random variation when calculating odds ratios based on smaller numbers, or a true limitation of excess risk to the uppermost two deciles (above 4900 ppm/days (13 ppm-years).

There were at least two possible biases which might have biased our results towards higher breast cancer rates among the more highly exposed. First, women with longer cumulative exposure tend to be those who worked longer (Spearman correlation, 0.36), and workers with longer employment may have had more screening via mammography because they had good medical surveillance and insurance coverage (although women who left employment with a study company may well have found other employment elsewhere with equally good medical

benefits). We had some limited data on mammography for live respondents. After excluding women with breast tumors lumps, or cysts, who would have had more mammograms subsequent to such problems, and after controlling for age, we did not find a strong association between cumulative exposure (in quintiles) and number of mammograms (0, 1-5, 6-10, 10+) via contingency table analysis (p=0.25). Furthermore the Spearman correlation coefficient between cumulative dose and number of mammograms (categories scored 0,1,2,3) was low, only 0.08. However, controlling for year of birth, women in the highest exposures category did have borderline significantly more mammograms (scored 0, 1, 2, 3) than those with lower exposures (p=0.06), using linear regression. The differences were not pronounced (eg., 39% of women in the highest exposure quintile had more than 5 mammograms, vs 30% of women in the low exposure quintile), and the R-square for this model was only 0.02. Restriction of the data to those with at least 5 years after exposure, when this possible bias might be expected to diminish, did not result in decreased exposure-response trends. All in all, there was no strong evidence (based on limited data) that this bias was important.

A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies under study, and hence greater cumulative exposure. Unfortunately, we did not have residential history, limiting our ability to explore this possibility. We did, however, compare the cumulative exposure of women whose cancers was ascertained via cancer registry (n=182) and women whose cancer was ascertained only via other records (n=137). Cumulative exposure was greater in the cases ascertained via cancer registry, but this difference was not statistically significant (p=0.13). Again, we did not

consider this to be strong evidence, based on limited data, for this potential bias.

Discussion

Our data do not indicate any overall excess of breast cancer incidence among the cohort as a whole compared to the U.S. population. However, cancer incidence was under-ascertained because of inability to locate some cohort members and because of incomplete coverage of the cohort by state cancer registries. We were able to contact only 68% of our cohort directly, and only about 50% of the cohort worked in states with cancer registries covering many years. It is not possible to accurately estimate the degree of under-ascertainment. Even with the under-ascertainment, however, we did find that the upper quintile of cumulative exposure, with a 15 year lag, had a 27% increase in breast cancer incidence compared to the SEER nonexposed population (34% after excluding in-situ cases).

Because of the issue of under-ascertainment, we have emphasized internal exposure-response analyses in our study rather than the use of external referent population. Exposure-response data do suggest an increased risk of incident breast cancer for those with higher cumulative exposures to ETO. This is especially apparent for exposures occurring 15 or more years before breast cancer occurrence.

Those in the top quintile of cumulative exposure, with a 15 year lag, showed an odds ratio of 1.74 (95% CI 1.16-2.65) in internal analyses based on all 319 cases compared with the lagged out group. The odds ratio was 1.87 (95% CI 1.12-3.10) in a similar analysis based on 233 cases with interview data, which controlled for parity and breast cancer in first degree relatives. Less excess risk for the upper quintile was seen without the lag. However, use of a lag is consistent

with a necessary latency period for solid tumors. The best fitting models for the exposure-response trend used a lag of 15 years and a log transformation of cumulative exposure, and showed statistically significant positive trends. The log transformation implies that rate ratios tend to flatten out or plateau at very high exposures, rather than increasing in a linear fashion. This phenomenon has been seen in other occupational carcinogens such as dioxin, silica, and diesel fumes[14-16], and has been discussed in detail in relation to arsenic[17].

There are two factors which tend to weaken the case for a causal relationship suggested by the positive exposure-response findings. One is that similar effects were seen using duration of exposure rather than cumulative exposure. This raises the possibility that some other factor related to duration of exposure could be associated with increased breast cancer risk, rather than cumulative exposure to ETO. Duration and cumulative exposure are moderately correlated (Spearman correlation coefficient 0.36), but not so strongly that an effect might not be seen for one variable and not the other. Secondly, the increase in risk does not appear to increase consistently (monotonically) with increasing cumulative exposure, but instead appears largely confined to those in the upper quintile of cumulative exposure.

On the other hand, there are counter-arguments to these weaknesses. Since duration of exposure is one component of cumulative exposure, the two are necessarily correlated, and it is not unexpected for exposure-response trends to exist for both measures. There are many uncertainties in estimating past exposures based on limited actual measurements. We did not have measured exposure levels for each person in our study, but instead estimated exposure levels over time based on existing measurement for different job categories. The method undoubtably led to errors in estimating exposure for individuals. Errors in estimating exposure

can lead to similar imprecision in estimating exposure-response trends. However, imperfect exposure estimation is typical of most retrospective epidemiologic studies. The exposure estimation for this cohort was based on a relatively large number of existing samples and is probably one of the better examples in the literature of retrospective exposure assessment. Our model predictions out-performed the best guesses of a panel of industrial hygienists assembled to evaluate our exposure prediction model[9].

Regarding the inconsistency of the exposure-response trend, it is not uncommon for such trends to exhibit fluctuations, some of which may be due to random variation, others of which might occur due to imprecision in estimating exposure.

In summary, our data do suggest that ETO is associated with breast cancer, but the case is not conclusive. Besides inconsistencies in the data for exposure-response, there are possible biases due to patterns of non-response and cancer ascertainment which introduce additional uncertainties in the findings.

References

1) NIOSH (1989), National Occupational Exposure Survey,: sampling methodology, DHHS publication NIOSH 89-102, Cincinnati, Ohio 1989

2) IARC (1994), Some industrial chemicals, Monograph 60, IARC, Lyon, France

3) Norman S, Berlin J, Soper K, Middendorf B, Stolley P (1995), Cancer incidence in a group of workers potentially exposed to ethylene oxide, Int J Epidemiol 24:276-284

4) Tompa A, Major J, Jakab M (1999), Is breast cancer cluster influenced by environmental and occupational factors among hospital nurses in Hungary?, Pathology Oncology Research 2: 117-121

5) Hagmar L, Welinder H, Linden K, et al.(1991), An epidemiological study of cancer risk among workers exposed to ETO using hemoglobin adducts to validate environmental exposure assessments, Occ Environ Health 63: 271-277

6) Hogstedt C, Aringer L, Gustavsson A (1986), Epidemiologic support for ETO as a cancer-causing agent, JAMA 255: 1575-1578

7) Gardner M, Coggon D, Pannett B, et al.(1989), Workers exposed to ETO: a follow-up study,

Brit J Ind Med 46: 860-865

8) Steenland K, Stayner L, Griefe A, Halperin B, Hayes R, Hornung R, Nowlin S (1991), A cohort mortality study of workers exposed to ethylene oxide, New Eng J Med 324,20: 1402-1407

9) Hornung R, Greife A, Stayner L, Steenland K, Herrick R, Elliott L, Ringenburg V, Morawetz J (1994), Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study, Am J Ind Med. 25:825-36.

10) Steenland K, Spaeth S, Cassinelli R, Laber P, Chang L, Koch K (1998), NIOSH Life Table Program for Personal Computers, Am J Ind Med 34: 517-518

11) SAS (1991), SAS User's Guide: Statistics (Version 6.07), SAS Institute Cary, NC

12) Steenland K and Deddens J (1997), Increased precision using counter-matching in nested case-control studies, Epidemiology 8: 238-242

13) Harrell F, Lee K, Pollock B (1988), Regression models in clinical studies: determining relationships between predictors and response, JNCI 80: 1198-1202

14) Steenland K, Deddens J, Piacitelli L (2001), Risk assessment for 2,3,7,8-*p*-dioxin (TCDD) based on an epidemiologic study, Am J Epidemiol 154: 451-458

15) Steenland K, Mannetje A, Boffetta P, Stayner L, Attfield M, Chen J, Dosemeci M, DeKlerk N, Hnizdo E, Koskela R, Checkoway H (2001), Pooled exposure-response and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multi-centric study, Cancer Causes Control 12: 773-784

16) Steenland K, Deddens J, Stayner L (1998), Diesel exhaust and lung cancer in trucking industry: exposure-response analyses and risk assessment, Am J Ind Med 34: 220-228

17) Hertz-Piccioto I and Smith A (1993), Observations on the dose-response curve for arsenic exposure and lung cancer, Scan J Work Environ Health 19:217-226

Table 1. Source of breast cancer cases (n=319)

Source (more than one source per case possible)	Number of cases identified by source (percent)
Death certificates	95 (30%)
Cancer registries	182 (57%)
Medical record*	144 (45%)
Interview (live)**	147 (46%)
Interview (dead)**	60 (19%)

* 85% with histopathology confirmation in the record
** 233 breast cancer cases or their next-of-kin had interviews. Medical record or cancer registry confirming their breast cancer was found for 189 of these (81%). Twenty-five interviews did not indicate that the respondent or the decedent (for next of kin interviews) had breast cancer on the interview (some next-of-kin did not answer this question), but breast cancer was found via medical record or cancer registry data. Six other women or their next-of-kin reported breast cancer on interview, but these reports were contradicted by medical record or cancer registry record; these women were therefore not considered cases.

Table 2. Description of cases and non-cases with interview data*

Variable	Cases (n=233)	Non-cases (n=4906)
% nulliparous	15.0%	11.6%
% with first-degree relative with breast cancer	16.3%	10.3%
% pre-menopausal at diagnosis	14.4%	n.a.
mean year of birth	1932 (s.d. 11.3)	1938 (s.d. 12.6)
mean number of children	2.29 (s.d. 3.52)	2.36 (s.d.3.34)
mean BMI age 20	20.8 (1.6)	21.0 (1.6)
median cumulative exposure	14.0 ppm-years	8.4 ppm-years

* Based on those with complete interview data for parity and breast cancer in first degree relatives. Somewhat fewer subjects had complete data for menopausal status and BMI.

Table 3. Rate ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), life table and Poisson regression analyses of entire cohort (n=7576)

	0 (lagged out)	<647	647-2026	2026-4919	4919-14620	>14620	combined exposed	test for trend, for cum.exp. or log cum.exp**.
15 yr lag								
external referent*	0.88(0.67-1.04)	0.77 (0.56-1.03)	0.77 (0.56-1.03)	0.94 (0.69-1.25)	0.83(0.61-1.11)	1.27 (0.94-1.69)	0.89 (0.78-1.01	linear, p=0.002 log, p=0.05
observed cases***	81	45	46	46	45	48	230	
		<855	855-2596	2596-6343	6343-16447	>16447		
no lag								
external referent*	n.a.	0.74 (0.57-0.97)	0.81 (0.62-1.04)	0.92 (0.70-1.18)	0.91 (0.70-1.17)	1.02 (0.79-1.30)	0.87 (0.77-0.97)	linear, p=0.16 log, p=0.08
observed cases		60	62	63	62	64	311	

- external referent is US population, SEER cancer incidence rates, 1970-1998, indirectly standardized incidence rate ratios (SIRs) stratified for age (5 year categories), ethnicity (white/nonwhite), and calendar time (5 year categories).

** test for trend (internal referent) calculated via Poisson regression, adjusted for age (5 year categories), calendar time (5 year categories), ethnicity (white/nonwhite)

*** 311 (of 319) cases were included; 8 cases were diagnosed before 1970 when SEER rates became available.

Table 4. Odds ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), Cox regression analyses* of entire cohort (n=7576, 319 cases)

exposure variable	model likelihood, d.f., p-value**	Coefficient, (std err), p-value	Odds ratios
categorical, cumulative exposure lagged 15 years (quintiles)***	17.8, 8 df, p=0.02	n.a.	1.00 (lagged out), 1.07 (0.72-1.59), 1.00 (0.67-1.50), 1.24 (0.85-1.90), 1.17 (0.78-1.78), 1.74 (1.16-2.65)
categorical, cumulative exposure, no lag (quintiles)***	10.4, 7 df, p=0.17	n.a.	1.00, 0.98 (0.69-1.38), 1.07 (0.76-1.51), 1.13 (0.80-1.59), 1.16 (0.82-1.65)
categorical, duration of exposure, lagged 15 years	20.5, 8 df, p=0.009	n.a.	1.00, 0.98 (0.66-1.45), 1.15 (0.77-1.73), 1.37 (0.91-2.04), 1.10 (0.73-1.67), 1.91 (1.22-2.15)
continuous, log cumulative exposure lagged 15 years	13.1, 4 df, p=0.01	0.037 (0.019), p=0.05	n.a.
continuous, log cumulative exposure	11.3, 4 df, p=0.02	0.049 (0.034), p=0.14	n.a.
continuous, cumulative exposure, lagged 15 years	11.2, 4 df, 0.02	0.0000054 (0.0000035), p=0.12	n.a.
continuous, cumulative exposure	9.3, 4 df, 0.05	0.0000013 (0.0000030), p=0.66	n.a.
continuous, duration exposure, lagged 15 years	14.5, 4 df., p=0.006	0.028 (0.02), p=0.02	n.a.
continuous, duration exposure	10.9, 4 df., p=0.03	0.012 (0.008), p=0.17	n.a.

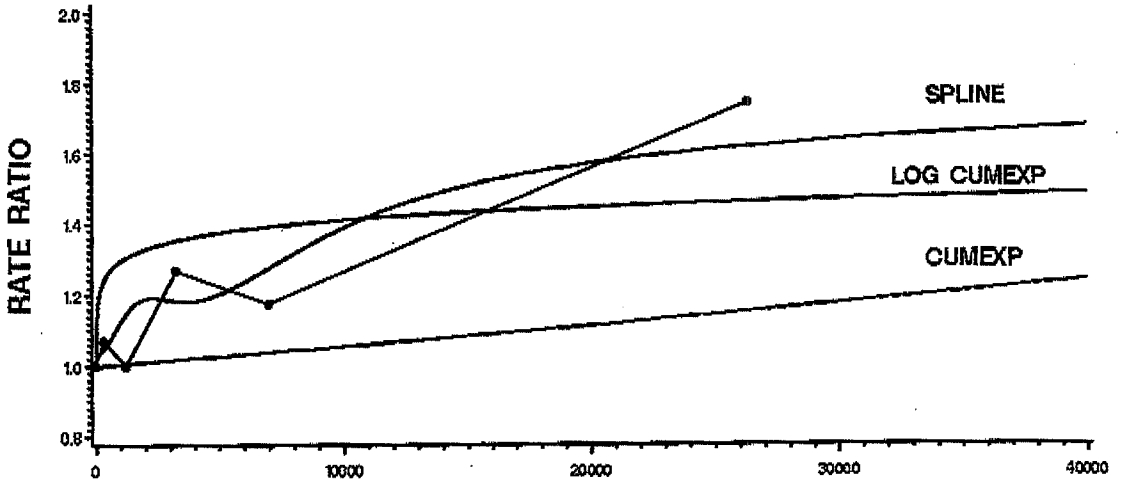
* odds ratios calculated via Cox regression, cases and controls matched on age, ethnicity (white/nonwhite), all models include cumulative exposure and categorical variable for year of birth (quartiles)
** model likelihood is difference in -2 log likelihoods between model with and without covariates
*** categories for cumulative exposure are the same as Table 3

Table 5. Odds ratios for breast cancer incidence by cumulative exposure to ETO (ppm-days), Cox regression analyses* of cohort with interviews (n=5139, 233 cases)

exposure variable	model likelihood, d.f., p-value**	Coefficient, (std err), p-value	Odds ratios by category***
categorical, cumulative exposure lagged 15 years (quintiles)***	27.8, 10 df, p=0.002	n.a.	1.00 (lagged out), 1.06 (0.66-1.71), 0.99 (0.61-1.60), 1.24 (0.76-2.00), 1.42 (0.88-2.29), 1.87 (1.12-3.10)
categorical, cumulative exposure, no lag (quintiles)	23.8, 9 df, p=0.005	n.a.	1.00, 1.25 (0.83-1.88) , 1.19 (0.78-1.83), 1.52 (1.00-2.29), 1.41 (0.92-2.16)
categorical, duration of exposure, lagged 15 years	32.3, 10 df, p=0.0004	n.a.	1.00, 1.00(0.63-1.60), 1.18 (0.73-1.90), 1.39(0.86-2.25), 1.11(0.67-1.82), 2.32 (1.37-3.94)
continuous, log cumulative exposure lagged 15 years	24.0, 6 df, p=0.0005	0.050 (0.023), p=0.03	n.a.
continuous, log cumulative exposure	24.4, 6 df, p=0.0004	0.092 (0.041), p=0.02	n.a.
continuous, cumulative exposure, lagged 15 years	23.4, 6 df, p=0.0007	0.0000095 (0.0000041), p=0.02	n.a.
continuous, cumulative exposure	21.6, 6 df., p=0.001	0.0000059 (0.0000035), p=0.10	n.a.
continuous, duration exposure, lagged 15 years	26.1, 6 df., p=0.0002	0.039 (0.014), p=0.006	n.a.
continuous, duration exposure	22.4, 6 df., p=0.001	0.019 (0.010), p=0.07	n.a.

* odds ratios calculated via Cox regression, cases and controls matched on age, ethnicity (white/nonwhite), all models include cumulative exposure and categorical variables for year of birth (quartiles), breast cancer in first degree relative, and parity
** model likelihood is difference in -2 log likelihoods between model with and without covariates
*** categories for cumulative exposure are the same as Table 3

ETO BREAST CANCER, 319 CASES
RATE RATIO vs CUMDOSE lag 15 yr
5 CATEGORIES, SPLINE, CUMEXP, LOG CUMEXP



Mortality analyses in a cohort of 18,235 ethylene oxide-exposed workers: followup extended from 1987 to 1998

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Abstract

Objectives: To extend mortality follow-up from 1987 to 1998 for cohort of 18,235 men and women exposed to ethylene oxide, a sterilant gas determined to be carcinogenic to humans by IARC in 1994 subsequent to findings of excess hematopoietic cancer in several cohorts. To investigate hematopoietic cancer mortality as well as breast cancer mortality, the latter of interest due to positive animal evidence and some limited epidemiologic evidence.

Methods: Standard mortality follow-up, life table and Cox regression analysis.

Results: We found a total of 2852 deaths, compared with 1177 in the earlier 1987 follow-up. We found no excess of hematopoietic cancers combined (SMR 1.00, 95% CI 0.82-1.20, 79 deaths) or of non-Hodgkin's lymphoma (SMR 1.00, 95 % CI 0.72-1.44, 31 deaths). However, detailed internal exposure-response analyses found positive trends for hematopoietic cancers which were limited to males (p=0.02 for log of cumulative exposure, 15 year lag). Analyses of lymphoid tumors (non-Hodgkin's lymphoma, myeloma, lymphocytic leukemia) indicated the hematopoietic excess was concentrated in these tumors (trend for cumulative exposure for both for males with a 15 year lag, p=0.02). Hematopoietic cancer trends were somewhat weaker in this analysis than trends in the earlier followup, and analyses restricted to the post-1987 data did not show any significant positive trends. Breast cancer did not show any overall excess (SMR 0.99, 95% CI 0.72-1.35, 103 deaths), although there was an excess in the highest cumulative exposure quartile using a 20 year lag (SMR 2.07, 95% CI 1.10-3.54). Internal exposure-response analyses found positive trend for breast cancer using the log of cumulative exposure with a 20 year lag (p=0.01)

Conclusions: Positive exposure-response trends for lymphoid tumors were found for males only. Reasons for the sex-specificity of this effect are not known. There is also some evidence of a positive exposure-response for breast cancer mortality.

Introduction

Ethylene oxide (ETO) is widely used as a sterilant gas and an industrial chemical. NIOSH has estimated that approximately 270,000 people were exposed in the US in the 1980s, principally in hospitals (96,000) and commercial sterilization (21,000)[1]. ETO is a direct-alkylating agent which causes increased chromosomal aberrations and sister-chromatid exchange[2]. Inhaled ETO is quickly absorbed in the lungs and distributed rapidly throughout all tissues; it forms dose-related hemoglobin adducts in people and rodents, and dose-related DNA adducts have been measured in rodents[2]. The International Agency for Research on Cancer (IARC) has determined that ETO is a definite (Group 1) human carcinogen, based on limited evidence from epidemiologic studies showing increased hematopoietic cancers which was supported by positive human cytogenetic evidence, and on sufficient evidence from animal studies for hematopoietic and other cancers[2].

Besides hematopoietic cancer, more recently there has been concern that ETO might also be linked to breast cancer, based on limited evidence. Norman et al.[3] found a statistically significant two-fold increase in breast cancer incidence based on 12 observed cases among women exposed at a plant doing commercial sterilization of medical products. A cluster of breast cancers was observed among Hungarian hospital workers exposed to ETO[4]. Furthermore, animal data indicated that ETO caused mammary tumors in mice[2], although not in rats. However, two other small incidence studies (together based on fewer than 10 cases) did not show an excess of breast cancer [5,6]. Two mortality studies, one small[7] (4 breast cancer deaths) and one large[5] (42 breast cancer deaths) also failed to show an excess.

In the mid 1980s the National Institute for Occupational Safety and Health (NIOSH) assembled a cohort of 18,235 workers exposed to ethylene oxide[8,9]. Results of the original followup through 1987 showed no overall excess of hematopoietic cancer, but did find a significant excess among men (SMR 1.55, 1.02-2.26), concentrated in non-Hodgkin's lymphoma[8]. Exposure-response analyses showed a significant positive trend with cumulative

exposure for lymphoid cancers (non-Hodgkin's lymphoma and lymphocytic leukemia, ICD 9th revision codes, 200, 202, 204), particularly among men.

We have updated the vital status of this cohort from 1987 to 1998. This resulted in 2852 deaths, a 140% increase over the 1177 deaths in the earlier followup. Analyses focused on hematopoietic and breast cancer mortality. A study of breast cancer incidence is the subject of a different paper[10].

Methods

Vital status followup was conducted through 1998 via the National Death Index (NDI), which provided cause of death, and via the Social Security Administration and the Internal Revenue Service (IRS). Person-time for each subject began 90 days after first exposure (due to a 3 month minimum for cohort eligibility), and continued until 12/31/1998, date of death, or date of lost-to-followup, whichever was earlier. Life table analyses were conducted using the NIOSH life-table program (Steenland et al. 1998), which provided results for 99 causes of death for the years 1960-1999. Deaths and person-time prior to 1960 were not included in this analysis, but there were only eight deaths before 1960 (0.2% of all deaths).

Exposure data over time for this cohort had been developed previously, based on a large number of measurements coupled with data of historical process changes, making it possible to quantitatively estimate cumulative exposure to ethylene oxide[11]. One small plant in the study (N=705, 4% of the cohort) lacked exposure estimates, and was excluded from exposure-response analyses.

Work history data had been gathered originally in the mid-1980s. Some plants in the study continued using ETO after this point. For those plants, we gathered additional information on the date-last-employed for those who had been employed and exposed at the time work history was collected (25% of the cohort). Work history for these individuals was extended until the date-last-employed at the plant; it was assumed that they did not change jobs and that

the level of ETO exposure remained the same as in their last job in the mid 1980s. This represented a compromise between an expensive and time-consuming effort to update all work histories in detail, and ignoring the incomplete histories altogether. In practice when we compared cumulative exposure calculated with and without the extended work histories, they differed little, largely because exposures were very low by the mid-1980s, so that the largest proportion of cumulative exposure came before those years.

Life table analyses were conducted for the entire cohort (n=18,235), using the U.S. population as the referent population[12]. Categorical analyses were done after categorizing the data by quartiles of cumulative exposure, based on distribution of cumulative exposure for either the deaths from either hematopoietic cancer or from breast cancer. The goal was to have approximately equal number of deaths from the principal causes of interest (hematopoietic and breast cancer) in each quartile, in unlagged analyses, thereby ensuring approximately equal precision of rate ratios. Life-table analyses were conducted using no lag, a 10 year lag for hematopoietic cancer, or a 20 year lag for breast cancer, prostate cancer, and kidney cancer. A 20 year lag discounts all exposure occurring with the last 20 years, and in some instances results in a case having no exposure ("lagged out"). These lags were chosen a priori as typical for hematopoietic tumors and solid tumors. Prostate and kidney cancer analyses were conducted based on finding slight excesses in the overall exposed vs. nonexposed analysis, rather than on a priori hypothesis; the same cutpoints were used in categorical analyses of cumulative exposure as were used for breast cancer, another solid tumor.

Internal exposure-response analyses were conducted using Cox regression for hematopoietic and breast cancer. Cox regression analyses were done using the SAS PHREG procedure[13]. In these analyses the time variable was age (effectively matching on age), and risk sets were constructed in which 100 randomly selected controls were chosen for each case from the pool of all those who survived without breast cancer to at least the age of the index case. Use of 100 controls has been shown to result in virtually the identical rate ratio with all possible

controls (the full risk set), with approximately the same precision[14], while making possible more rapid computer runs. Cases and controls were matched on race (white/non-white), sex, and date-of-birth (within 5 years), and only exposure variables were included in models. Matching on date-of-birth, in combination with the use of age as the time variable to form risk set, was equivalent to matching on calendar time. Exposure in these analyses was time-dependent, and was truncated if it extended beyond the age of the case failure.

Internal analyses focused on cancers of a priori interest, i.e., all hematopoietic cancers and breast cancer. We also analyzed a lymphoid cell line tumors as a group, under the hypothesis that these tumors might share a common etiology. In previous analyses[9] we had included as lymphoid tumors both non-Hodgkin's lymphoma and lymphocytic leukemia (9th revision ICD codes 200, 202, and 204), and we again have provided some results for that original grouping. However, we have now also conducted analyses after adding myeloma (ICD code 203) to the lymphoid group, based on current thinking on this issue [15,16] (personal communication Bernard Goldstein, Univ of Pittsburgh, 2002). Another complication was that 4/25 (16%) leukemias in the exposure-response analyses were classified as "not specified", some of which might have been lymphocytic leukemia. Finally, a separate analysis was also done of Hodgkin's disease (ICD 201).

Exposure-response analyses focused on cumulative exposure or the log of cumulative exposure, with or without a lag for exposure (5, 10, 15, and 20 year lags were tried). We added 1 ppm-day to cumulative exposure in lagged analyses to avoid taking the log of 0. In the results we present only the lagged model with the best fit to the data, as judged by the likelihood ratio test. We also tried models using peak exposure, average exposure, and duration of exposure, with no lag or different lags. Test of significance for the coefficients of continuous exposure variables (tests for trend) were based on the likelihood ratio statistic rather than the Wald statistic.

Results

Cumulative exposure average 26.9 ppm-years in this cohort (std. dev. 65.7), with a highly skewed distribution (median 5.6 ppm-years). Exposure for males (mean 37.8, std. dev. 87.6, median 7.6) was higher than for females (mean 18.2, std.dev. 38.2, median 4.6), largely because of their more frequent employment in high exposure jobs such as sterilizer operator or warehouse employee. There were 461,000 person years of follow-up; mean follow-up time from first employment was 26.8 years (std.dev. 8.5). Sixteen percent of the cohort died during follow-up, which ended in 12/31/1998. Of the decedents, 1.5% (n=44) were missing cause of death.

Table 1 gives the overall mortality results for the entire cohort, compared to the U.S. population. No cancer site showed a significant excess at the 0.05 level, with the exception of bone cancer, for which there were only six deaths. Neither all hematopoietic cancer nor non-Hodgkin's lymphoma show any elevation. In sex-specific analyses, the rate ratios for men for all hematopoietic cancer, leukemia, and non-Hodgkin's lymphoma were 1.09 (0.79-1.47), 0.97 (0.53-1.63), and 1.29 (0.78-2.01) respectively, while the corresponding rate ratios for women were 0.90 (0.64-1.25), 1.02 (0.57 1.68), and 0.73 (0.38-1.28). Brain cancer mortality, which of some a priori interest due to positive animal studies, was significantly reduced in this update, similar to findings in our prior followup. Prostate and kidney cancer showed slight elevations (SMR 1.29 (95% CI 0.96-1.70, 37 deaths) and 1.19 (95% CI 0.80-1.72, 21 deaths), respectively), motivating further life table exposure-response analyses.

Exposure-response analyses were of limited value for bone cancer due to the small number of deaths. Life table analyses of bone cancer using the cumulative exposure categories for hematopoietic cancer (0-1,200, 1,200-3,080, 3,080-13,500, 13,500+ ppm-days) showed SMRs of 1.47 (95% CI 0.04-8.19), 7.14 (95% CI 1.47-20.80), 5.41 (95% CI 0.66-19.5) and 0 based on 1, 3, 2, and 0 observed deaths in ascending quartiles of cumulative exposure. This pattern in not particularly supportive of a positive exposure response.

Table 2 shows the analyses by quartile of cumulative exposure for all hematopoietic

cancer, with the quartiles chosen in order to approximately distribute the hematopoietic deaths equally by quartile. There is no suggestion of a trend for all hematopoietic cancers combined or any specific category, with the exception of Hodgkin's disease where inference is limited by the small number of deaths. Table 3 shows the same analyses with a 10 year lag. Here is the highest quartile of cumulative exposure shows a somewhat elevated rate ratio for non-Hodgkin's lymphoma, based on nine deaths.

Tables 4 and 5 show the data for hematopoietic cancer by sex, with no lag and with a 10 year lag. The only statistically significant excess, at the 0.05 level, is the SMR for males for non-Hodgkin's lymphoma in the uppermost exposure quartile with a 10-year lag (SMR 2.37, 95% CI 1.02-4.67, 8 deaths). Five of the six Hodgkin's disease deaths occurred among males, and this outcome again shows a positive exposure-response based on very small numbers.

Table 6 shows the data for cumulative exposure and breast, prostate, and kidney cancer morality. The quartiles for these analyses used the quartile cutpoints which allocated breast cancers equally by quartile. In this analysis there is an indication of excess risk for breast cancer in the uppermost quartile, which is 2.20 (95% CI 1.57-2.98) using a 20-year lag. There was little or no suggestion of positive exposure-response trends for prostate or kidney cancer.

Tables 7 and 8 show the results of internal Cox regression analyses for all hematopoietic cancers combined and for lymphoid cell line tumors, for both sexes combined and for men and women separately. Table 7 indicates that only males show a positive trends. The best fitting model shows a positive trend (p=0.02) for males using the log of cumulative exposure with a 15 year lag (the best fitting model). The log transformation tends to give less influence in the model to very high exposures typical of skewed exposure distributions, which may improve model fit. It also usually implies that rate ratios tend to flatten out or plateau at higher exposures, rather than increasing in a linear fashion, which is apparent in our own data here for males. Categorical analyses by quartile for males indicated that all three upper quartiles were elevated compared to the lowest category, parallel to the life table results in Table 4. Categorical

analyses using cumulative exposure with a 15 year lag shows a more monotonically increasing trend.

Although not shown, models using duration of exposure, peak exposure, and average exposure did not predict hematopoietic cancer as well as models using cumulative exposure.

Table 8 shows a positive trend for lymphoid tumors (non-Hodgkin's lymphoma, myeloma, and lymphocytic leukemia) with cumulative exposure for both sexes combined ($p=.08$), which was again concentrated in for males ($p=0.06$ for cumulative exposure and $p=0.02$ for log cumulative exposure, 15 year lag, the latter being the best fitting model). Although not shown, models using duration of exposure, peak exposure, and average exposure did not predict hematopoietic cancer as well as models using cumulative exposure.

Additional analyses (not shown) were conducted using a more restricted definition of lymphoid tumors (non-Hodgkin's lymphoma and lymphocytic leukemia, n=40, 23 male and 17 female deaths) to conform to our earlier analysis of this cohort[9]. The coefficient for cumulative exposure with no lag was 5.6×10^{-6} (s.e. 2.3×10^{-6}, $p=0.04$ based on change in likelihood), decreased from 9.0×10^{-6} in our earlier follow-up which ended in 1987. Best-fitting lagged models were either cumulative exposure with a 5 year lag (coefficient 6.1×10^{-6}, s.e. 2.5×10^{-6}, $p=0.04$) or log cumulative exposure with a 15 year lag (coefficient 0.11, s.e. 0.05, $p=0.04$). The former model in our earlier analysis had a coefficient about twice as large (1.29×10^{-5}). The effect was again concentrated in males (coefficient for cumulative exposure 6.0×10^{-6}, s.e. 2.3×10^{-6}, $p=0.03$). The best fitting model for males used the log of cumulative exposure with a 15-year lag (coefficient 0.169, s.e. 0.066, $p=0.008$).

Additional analyses (not shown) were conducted for Hodgkin's disease, based on only six deaths. A positive trend ($p=0.08$) was found for the log of cumulative exposure with a lag of 10 years, for both sexes combined. This excess also was concentrated in males (5 of 6 deaths).

Additional regression analyses, not shown, were restricted to the period following 1987, the end of the prior followup. In these post-1987 analyses there were no significant positive

trends for all hematopoietic cancer (n=41), male hematopoietic cancer (n=13), lymphoid cancers (n=31), or male lymphoid cancers (n=10). The analyses restricted to males did show a suggestion of increased hematopoietic cancer, but analyses were limited by small numbers. For example, in categorical analyses there was only one case in the lowest quartile, making odds ratios unstable. Collapsing, the odds ratio for the two top quartiles vs the two bottom ones was 1.46 (0.45-4.78). The coefficient for male hematopoietic cancer for log cumulative exposure with a 15 year lag was 0.11 (s.e. 0.12, p=0.35), about the same value as that for the entire followup period (Table 7).

Table 9 gives the results for internal Cox regression analyses for breast cancer. The best model using a continuous exposure variable was that using the log of cumulative exposure with a 20 year lag (p=0.01). Cumulative exposure itself did not show a strong trend (p=0.16). Categorical analysis of lagged data (20 year lag) showed an increased rate in the highest quartile (3.13, 95% CI 1.42, 6.92).

Discussion

Ethylene oxide has been studied in 10 cohort studies with over 33,000 workers; among these the largest component is the cohort studied here (18,000). Results of these studies as of 1998 have been reviewed by Teta et al.[17]. Generally cancer findings were unremarkable in comparisons of exposed workers to the general population for most of these studies, with the notable exception of large excesses of hematopoietic cancer (particularly leukemia) in several early small studies from Sweden. However, a meta-analysis of all 10 studies did show an increase in non-Hodgkin's lymphoma (1.34, 95% CI 0.96-1.89), based on 33 deaths. A combined analysis of two studies with exposure-response data (the 18,000 workers in the NIOSH study followed through 1987, and 1,900 chemical production workers[18]) showed positive significant trends for leukemia but was inconsistent for lymphoid tumors (NHL plus lymphocytic leukemia), with significant positive trends in the NIOSH cohort and negative trends

(based on small numbers) among the chemical workers[17].

We have now updated mortality followup for the large NIOSH cohort of 18,000 workers exposed to ethylene oxide, adding 11 more years of follow-up and more than doubling the number of deaths. Hematopoietic cancer (particularly among males) and breast cancer among females showed some association with ethylene oxide exposure. Bone cancer was in excess compared to the US population based on only six deaths, but did not show an increase with increasing exposure. There is some supporting animal evidence in that mice injected subcutaneously developed local sarcomas[2], which share the mesenchymal cell origin of bone tumors. However, due the small number of bone cancer deaths, and the lack of exposure-response, no conclusions can be drawn from this excess. No other cancer site was in excess in the cohort.

Regarding hematopoietic cancer, we did not find an overall excess of hematopoietic cancer or any specific type of hematopoietic cancer. However, we did find statistically significant exposure-response trends for male hematopoietic cancer, particularly lymphoid tumors. These findings are consistent with analyses of this cohort with earlier followup[9]. Exposure-response coefficients were somewhat smaller than we found in our earlier analyses (analyses restricted to recent years did not show significant positive exposure-response trends). This suggests that any ETO damage to the hematopoietic system may be decreasing over time.

It is not known why we find an association for males and not females for hematopoietic cancer. While males on the average did have higher exposure than females because they were over-represented in high exposure jobs (eg., sterilizer operator), there was sufficient variation in the exposure of women to have observed an exposure-response if one existed. Animal data do not support a sex-specific effect for leukemia.

The increasing trends in rate ratios for hematopoietic cancer for males tended to tail off or plateau at high exposure (as is implied by the better model fit using a log transformation of cumulative exposure). This phenomenon has been seen in other occupational carcinogens such

as dioxin[19], silica[20], and diesel fumes[21], and has been discussed in detail in relation to arsenic[22]. Possible reasons for this phenomenon include, among others: 1) a depletion of susceptibles at high exposures, 2) the healthy worker survivor effect, 3) misclassification of high exposures, and 4) a saturation of metabolic pathways.

We found no overall excess of breast cancer mortality, but we did find a suggestive positive trend with increasing cumulative exposure, particularly after taking into account a 20 year lag period. Mortality is a less sensitive endpoint than incidence for breast cancer. We have also recently completed a study of breast cancer incidence in this cohort, results of which are to be published separately.

This study had a number of limitations, including the reliance on small numbers to make inferences about hematopoietic cancers, uncertainties in the retrospective estimation of exposure, and the use of mortality data rather than incidence data for evaluation of cancer risk. On the other hand, this is by far the largest existing cohort of ETO workers, the 11 year update has added substantially more deaths, and retrospective exposure estimation for this study was based on a large number of observed industrial hygiene samples and a well-validated model to estimate past exposures. Mortality data for hematopoietic cancer might be expected to give similar results to incidence data, as these cancers are often fatal. For breast cancer, we are conducting a separate and parallel study of cancer incidence.

In conclusion, we found no overall evidence of excess cancer mortality in this cohort, with the exception of bone cancer for which there did not appear to be a positive exposure-response relationship. In exposure-response analyses we found evidence of an association between increased exposure and some types of hematopoietic cancer, particularly for males, and particularly for earlier followup years. There is also some positive but not conclusive evidence in exposure-response analyses for breast cancer mortality.

References

1) NIOSH (1989), National Occupational Exposure Survey,: sampling methodology, DHHS publication NIOSH 89-102, Cincinnati, Ohio

2) IARC (1994), Some industrial chemicals, Monograph 60, IARC, Lyon, France

3)Norman S, Berlin J, Soper K, Middendorf B, Stolley P (1995), Cancer incidence in a group of workers potentially exposed to ethylene oxide, Int J Epidemiol 24:276-284

4) Tompa A, Major J, Jakab M (1999), Is breast cancer cluster influenced by environmental and occupational factors among hospital nurses in Hungary?, Pathology Oncology Research 2: 117-121

5) Hagmar L, Welinder H, Linden K, et al.(1991), An epidemiological study of cancer risk among workers exposed to ETO using hemoglobin adducts to validate environmental exposure assessments, Occ Environ Health 63: 271-277

6) Hogstedt C, Aringer L, Gustavsson A (1986), Epidemiologic support for ETO as a cancer-causing agent, JAMA 255: 1575-1578

7) Gardner M, Coggon D, Pannett B, et al.(1989), Workers exposed to ETO: a follow-up study, Brit J Ind Med 46: 860-865

8) Steenland K, Stayner L, Griefe A, Halperin B, Hayes R, Hornung R, Nowlin S (1991), A cohort mortality study of workers exposed to ethylene oxide, New Eng J Med 324,20: 1402-1407

9) Stayner L, Steenland K, Greife A, Hornung R, Hayes R, Nowlin S, Morawetz J, Ringenburg V, Elliot L, and Halperin H (1993), Exposure-response analyses of cancer mortality in a cohort of workers exposed to ethylene oxide, Am J Epidemiol 138, 787-798

10) Steenland K, Whelan E, Deddens J, Stayner L, Ward L (2002), Ethylene oxide and breast cancer incidence in a cohort study of 7576 women, submitted

11) Hornung R, Greife A, Stayner L, Steenland K, Herrick R, Elliott L, Ringenburg V, Morawetz J (1994), Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study, Am J Ind Med. 25:825-36.

12) Steenland K, Spaeth S, Cassinelli R, Laber P, Chang L, Koch K (1998), NIOSH Life Table Program for Personal Computers, Am J Ind Med 34: 517-518

13) SAS (1991), SAS User's Guide: Statistics (Version 6.07), SAS Institute Cary, NC

14) Steenland K and Deddens J (1997), Increased precision using counter-matching in nested case-control studies, Epidemiology 8: 238-242

15) Cotran R, Kumar V, Collins T (eds)[1999], Pathologic basis of disease, Saunders, Philadelphia

16) Harris N, Jaffe E, Diebold J, Flandrin G, Muller-Hermelink K, Vadiman J, Listrer T, Bloomfield C(1999), WHO classification of neoplastic diseases of the hematopoietic and lymphoid tissues, J Clin Oncol 17: 3835-3849

17) Teta J, Sielken R, and Valdez-Flores C (1999), Ethylene oxide cancer risk assessment based on epidemiologic data: application of revised regulatory guidelines, Risk Analysis 19: 1135-1155

18) Teta J, Benson O, Vitale J (1993), Mortality study of ethylene oxide workers in chemical manufacturing: a 10 year update, Br J Ind Med 50: 704-709

19) Steenland K, Deddens J, Piacitelli L (2001), Risk assessment for 2,3,7,8-*p*-dioxin (TCDD) based on an epidemiologic study, Am J Epidemiol 154: 451-458

20) Steenland K, Mannetje A, Boffetta P, Stayner L, Attfield M, Chen J, Dosemeci M, DeKlerk N, Hnizdo E, Koskela R, Checkoway H (2001), Pooled exposure-response and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: an IARC multi-centric study, Cancer Causes Control 12: 773-784

21) Steenland K, Deddens J, Stayner L (1998), Diesel exhaust and lung cancer in trucking industry: exposure-response analyses and risk assessment, Am J Ind Med 34: 220-228

22) Hertz-Piccioto I and Smith A (1993), Observations on the dose-response curve for arsenic exposure and lung cancer, Scan J Work Environ Health 19:217-226

Table 1. Mortality in the ETO cohort (n=18,235)

	observed deaths	SMR (95% CI)	male SMR (95% CI)	female SMR (95% CI)
all causes	2852	0.90 (0.88-0.93)	0.94 (0.89-0.99)	0.86 (0.81-0.91)
coronary heart disease (410-414)	669	0.92 (0.86-0.98)	1.04 (0.85-1.04)	0.87 (0.78-0.99)
all cancers (140-208)	860	0.98 (0.92-1.03)	0.94 (0.95-1.16)	0.92 (0.84-1.01)
stomach (151)	25	1.07 (0.74-1.49)	0.87 (0.44-1.52)	1.34 (0.71-2.29)
pancreas (157)	38	0.92 (0.69-1.21)	1.03 (0.64-1.61)	0.82 (0.45-1.30)
lung (162)	258	1.05 (0.95-1.17)	1.05 (0.89-1.23)	1.05 (0.86-1.27)
prostate (185)	37	1.29 (0.91-1.78)	1.29 (0.91-1.78)	n.a.
kidney (189.0-189.2)	21	1.19 (0.80-1.72)	1.51(0.85-2.49)	0.78 (0.281.28)
brain (191-192)	14	0.59 (0.36-0.91)	0.52 (0.19-1.13)	0.65 (0.25-7.37)
bone (170)	6	2.82 (1.23-5.56)	3.51 (0.96-8.98)	2.04 (0.25-7.37)
breast cancer (174)	103	0.99 (0.84-1.17)	2.04 (0.05-11.37)	0.99 (0.81-1.20)
all hematopoietic (200-208)	79	1.00 (0.79-1.24)	1.09 (0.79-1.47)	0.91 (0.84-1.25)
non-Hodgkin's lymphoma (200, 202)	31	1.00 (0.72-1.35)	1.29 (0.78-2.01)	0.73 (0.38-1.29)
Hodgkin's disease (201)	6	1.24 (0.53-2.43)	1.83 (0.59-4.27)	0.47 (0.05-11.87)
myeloma (203)	13	0.92 (0.54-0.87)	0.61 (0.17-1.56)	1.19 (0.54-2.26)
leukemia (204-208)	29	0.99 (0.71-1.36)	0.97 (0.52-1.63)	1.02 (0.57-1.68)

Table 2. SMRs (observed deaths) by cumulative exposure for hematopoietic cancer (ICD 9th revision 200–208), no lag (n=17,530)

cause	0-1200 ppm-days	1200-3680 ppm-days	3680-13500 ppm-days	13500+ ppm-days
all hematopoietic	0.77 (18)	1.31 (20)	1.10 (18)	0.94 (18)
NHL	0.76 (7)	1.34 (8)	0.85 (6)	1.21(9)
Hodgkin's	0 (0)	0.99 (1)	2.97 (3)	2.20 (2)
Leukemia	1.15 (10)	1.06 (6)	0.93 (6)	0.43 (3)
Myeloma	0.26 (1)	1.89 (5)	0.92 (3)	1.03 (4)

Table 3. SMRs (observed deaths) by cumulative exposure for hematopoietic cancer, 10 year lag (n=17,530)

cause	0 (lagged out)	>0-1200 ppm-days	1200-3680 ppm-days	3680-13500 ppm-days	13500+ ppm-days
all hematopoietic	0.72 (9)	0.88 (18)	1.16 (15)	1.08 (16)	1.04 (16)
NHL	1.31 (5)	0.71 (6)	1.13 (6)	0.66 (4)	1.47 (9)
Hodgkin's	0.41 (1)	0 (0)	1.75 (1)	3.57 (2)	3.77 (2)
Leukemia	0.40 (2)	1.35 (10)	0.85 (4)	1.33 (7)	0.36 (2)
Myeloma	1.36 (1)	3.65 (2)	2.44 (4)	1.03 (3)	0.92 (3)

Table 4. SMRs (observed deaths) by cumulative exposure for hematopoietic cancer mortality, by sex, no lag

cause	0-1200 ppm-days	1200-3680 ppm-days	3680-13500 ppm-days	13500+ ppm-days
males (n=7645)				
all hematopoietic	0.54 (5)	1.16 (8)	1.28 (10)	1.28 (14)
NHL	0.83 (3)	1.14 (3)	1.34 (4)	1.97 (8)
Hodgkin's	0 (0)	1.89 (1)	3.70 (2)	3.28 (2)
Leukemia	0.57 (2)	0.76 (2)	1.37 (4)	0.49 (2)
Myeloma	0 (0)	1.78 (2)	0 (0)	0.92 (2)
females (n=9885)				
all hematopoietic	0..92(13)	1.43 (12)	0.80 (8)	0.48 (4)
NHL	0.72 (4)	1.49 (5)	0.49 (2)	0.30 (1)
Hodgkin's	0 (0)	0 (0)	0.47 (1)	0 (0)
Leukemia	1.54 (8)	1.32 (4)	0.56 (2)	0.35 (1)
Myeloma	0.40 (1)	1.97 (3)	1.59 (3)	1.17 (2)

Table 5. SMRs (observed deaths) by cumulative exposure, for hematopoietic cancer mortality, by sex, 10 year lag

cause	0 (lagged out)	>0-1200 ppm-days	1200-3680 ppm-days	3680-13500 ppm-days	13500+ ppm-days
males (n=7645)					
all hematopoietic	1.15 (7)	0.63 (5)	0.87 (5)	1.10 (7)	1.46 (13)
NHL	2.09 (4)	0.61 (2)	0.88 (2)	0.79 (2)	2.37* (8)
Hodgkin's	1.07 (1)	0 (0)	3.44 (1)	3.44 (1)	5.71 (2)
Leukemia	0.41 (1)	1.01 (3)	0.0 (0	1.70 (4)	0.60 (2)
Myeloma	1.56 (1)	0 (0)	1.94 (2)	0 (0)	0.54 (1)
females (n=9885)					
all hematopoietic	0.31 (2)	1.04 13)	1.38 (10)	1.06 (9)	0.46 (3)
NHL	1.88 (1)	0.78 (4)	1.32 (4)	0.56 (2)	0.37 (1)
Hodgkin's	0 (0)	0 (0)	0 (0)	3.70 (1)	0 (0
Leukemia	0 (0)	0.57 (7)	1.56 (4)	1.02 (3)	0 (0)
Myeloma	1.56 (1)	0.85 (2)	1.42 (2)	1.76 (3)	1.43 (2)

*95 % CI 1.02-4.67

Table 6. SMRs (observed deaths) by cumulative exposure, for breast cancer, prostate cancer, and kidney cancer, no lag and 20 year lag

cause	0 (lagged out)	>0-647 ppm-days	647-2780 ppm-days	2780-12322 ppm-days	12322+ ppm-days
breast-no lag (females only)		1.00 (26)	0.85(24)	0.92 (26)	1.27 (26)
prostate- no lag		1.74 (6)	1.47 (8)	0.77 (5)	1.33 (15)
kidney- no lag		0.88 (3)	0.74 (3)	1.36 (6)	1.06 (5)
breast-20 year lag (females only)	0.80 (42)	1.05 (17)	1.01 (15)	1.15 (15)	2.07* (13)
prostate-20 year lag	1.08 (8)	1.43 (5)	1.44 (6)	1.75 (8)	1.00 (7)
kidney- 20 year lag	0.70 (2)	0.28 (1)	1.62 (6)	2.11 (8)	0.99 (5)

* 95% CI 1.10-3.54

Table 7. Cox regression* results for all hematopoietic cancer mortality

Analysis, exposure variable	model likelihood, d.f., p-value**	Coefficient, (std err)	Odds ratios by category***
Both sexes, Cumulative exposure	1.62, 1 df, p=0.20	0.0000033 (0.0000023)	
Males, Cumulative exposure	2.45, 1 df, p=0.12	0.0000040 (0.0000022)	
Males, Categorical cumulative Exposure	2.53, 3 df, p=0.46	n.a.	1.00, 2.07 (0.67-6.41), 2.02 (0.68-5.98), 2.06 (0.72-5.91)
Females, Cumulative exposure,	0.87, 1 df, p=0.34	-0.000011 (0.000014)	
Females, Categorical cumulative Exposure	3.78, 3 df, p=0.29	n.a.	1.00, 1.51 (0.69-3.34), 0.93 (0.38-2.30), 0.52 (0.16-1.66)
Males, Log cumulative exposure, 15 year lag	5.29, 1 df, p=0.02	0.119 (0.052)	
Males, Categorical cumulative Exposure, 15 year lag	6.81, d.f.=4 p=0.15	n.a.	1.00, 1.23 (0.32-4.73), 2.52 (0.69-9.22), 3.13 (0.95-10.37, 3.42 (1.09-10.73)

* Cases and controls matched on age, race (white/nonwhite), date of birth within 5 years , 74 cases (37 male, 37 female)

** model likelihood is difference in -2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p-value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend

*** categories for cumulative exposure are the same as Tables 2-5

Table 8. Cox regression results for lymphoid cell-line tumors*

Analysis, exposure variable	model likelihood, d.f., p-value**	Coefficient, (std err)	Odds ratios by category***
Both sexes, Cumulative exposure	3.16, 1 df, p=0.08	0.0000046 (0.0000022),	n.a.
Males, Cumulative exposure	3.62 1 df, p=0.06	0.0000050 (0.0000022)	n.a.
Males, Categorical cumulative Exposure	2.43, 3 df, p=0.49	n.a.	1.00, 2.45 (0.61-9.92, 1.85 (0.46-7.48), 2.44 (0.67-8.87)
Females, Cumulative exposure	0.08, 1 df, p=0.78	-0.0000034 (0.000012)	n.a.
Females, Categorical , Cumulative exposure	2.81, 3 df, p=0.42	n.a.	1.00, 2.05 (0.76-5.56), 1.25 (0.40-3.76), 0.87 (0.24-3.10)
Males, log Cumulative exposure, 15 year lag	5.39, 1df, p=.02	0.138 (0.061)	n.a.
Males, Categorical cumulative Exposure, 15 year lag	6.62, 4 df, p=0.13	n.a.	1.00, 0.90 (0.16-5.24), 2.89 (0.65-12.86) 2.74 (0.65-11.55), 3.76 (1.03-13.64)

* Lymphoid cell line tumors include NHL, myeloma, and lymphocytic leukemia (ICD 9th revision codes 200, 202, 203, 204 (53 cases, 27 male, 26 female). Cox regression, cases and controls matched on age, race (white/nonwhite), date of birth within 5 years

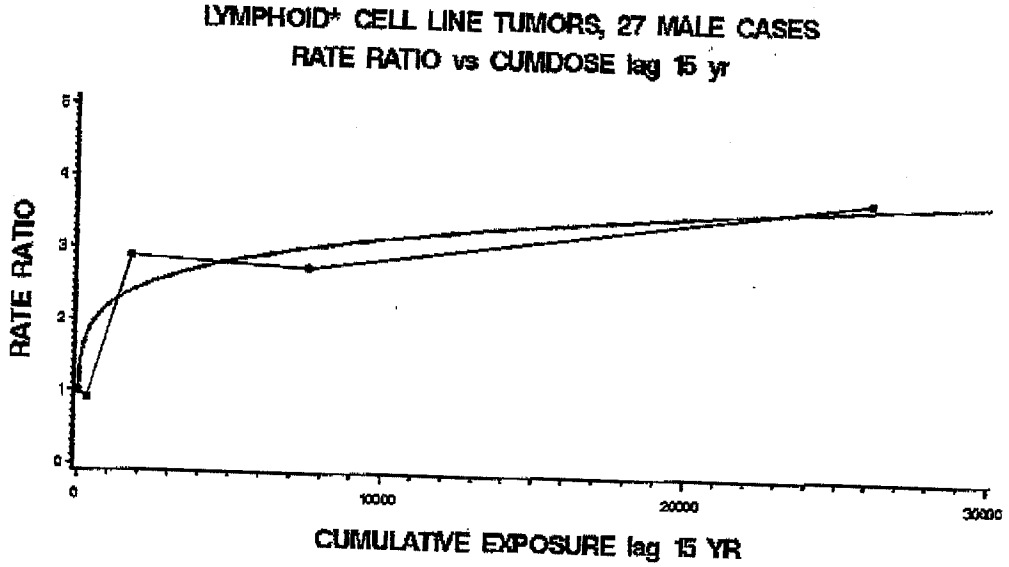
** model likelihood is difference in -2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p-value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend

*** categories for cumulative exposure are the same as Tables 2-5

Table 9. Cox regression results for breast cancer mortality*

Analysis, exposure variable	model likelihood, d.f., p-value**	Coefficient, (std err)	Odds ratios by category***
Cumulative exposure	0.88, 1 df, p=0.34	0.0000049 (0.0000048,	n.a.
Log cumulative exposure, 20 year lag	5.69, 1df, p=.01	0.084 (0.035),	n.a.
Categorical cumulative Exposure lagged 20 years (quartiles)	8.69, 4 df, p=0.07	n.a.	1.00, 1.76 (0.91-3.43), 1.77 (0.88-3.56), 1.97 (0.94-4.06), 3.13 (1.42-6.92)

* There were 103 cases of breast cancer (ICD 9th 174, 175). In Cox regression, cases and controls were matched on age, race (white/nonwhite), and date of birth within 5 years
** model likelihood is difference in -2 log likelihoods between model with and without covariates; the only covariate in these models was exposure, so the p-value of the model serves as a test of significance of the exposure coefficient, and as a test of exposure-response trend,
*** categories for cumulative exposure are the same as Table 6



*ICD9 codes 200,202,203,204